# LETTERS *to the Editor*

## Metronidazole for Trichomonas Infections

TO THE EDITOR: I read with great interest the article entitled "Infectious Urethritis in Men and Women" by Dr. Edwin M. Meares, Jr., in the December 1975 issue of THE WESTERN JOURNAL OF MEDICINE (123:436-441, Dec 1975).

In particular I make reference to the treatment regimen for trichomonas urethritis in which Dr. Meares does not suggest an alternate other than metronidazole in the management of that disease. In a letter dated October 27, 1974 to the Commissioner of Food and Drug Administration by the Health Research Group of Washington, D.C., they urged the FDA to take prompt action against the use of metronidazole because of its potential as a carcinogenic agent in rodents and mutagenic in bacteria. In addition the medical letter of June 1975 states, "It should not be used, i.e., metronidazole, for trichomonas infections that can be made asymptomatic by other means." This is rather strong language and as an internist I would like to know from Dr. Meares if there is an effective alternate form of treating both sexual partners who have trichomonas urethritis.

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### The Author Replies

I WELCOME the opportunity of responding to Dr. Grabowski's letter and his questions regarding the use of metronidazole (Flagyl®) for the treatment of genitourinary tract infections in men and women due to Trichomonas vaginalis. Many physicians are aware of the studies conducted in laboratory animals that have shown a carcinogenic potential of metronidazole in those animals that were studied. Many physicians are also aware of the recommendation that was made by the Health Research Group of Washington, D.C., to the United States Food and Drug Administration (FDA) in petitions dated March 20, 1974 and October 22, 1974 that metronidazole be withdrawn as an approved agent in the treatment of trichomonal vaginitis. Unfortunately, to my knowledge, the results of the hearings and extensive research that were conducted by the Food and Drug Administration regarding the use of metronidazole in human patients have never been published in any journal or news media that has been readily available to the medical profession.

On October 21, 1975 Dr. Alexander M. Schmidt, Commissioner of the FDA, forwarded to the Health Research Group of Washington, D.C., the results and conclusions of the FDA's investigations regarding the use of metronidazole. Under the Freedom of Information Act, this document is public property and can be freely quoted without special permission. In fact, I have been informed by the FDA that copies of this letter have been sent out extensively to members of the medical profession who have made inquiries regarding this matter and that the FDA plans to send out a printed summary of this letter to various members of the medical profession in this country in the near future.

At this time Dr. Grabowski's questions can best be answered by the following direct quote from the conclusions made in the letter cited above by Dr. Alexander Schmidt to the Health Research Group of Washington, D.C.:

"The FDA shares your concern over the carcinogenicity of metronidazole in rodents. Nevertheless, the available evidence indicates that the total dose of metronidazole given to patients is of such low order of magnitude when compared to the life-span doses given to rodents, that the element of carcinogenic risk in treating trichomoniasis is very low.

"Further, it is our conclusion, which is shared by many experts and by our OB-GYN Advisory Committee, that Trichomonas vaginitis is an important disease causing much suffering among its victims, and that metronidazole is the only drug currently marketed in this country which is effective in its cure.

"We therefore conclude that benefits-risk considerations at this time indicate that metronidazole should continue to be available for the treatment of trichomoniasis, with labeling which includes an adequate discussion of animal carcinogenicity and possible carcinogenic hazard to humans and provides guidance on appropriate uses of the drug. The labeling is currently undergoing revision with

respect to the indications and warnings section, and a box warning is being developed.

"Finally, we believe it will prove possible to reduce the amount of nitroimidazole used in treatment. Studies of a single-dose regimen of tinidazole will therefore be permitted to proceed. Further, the effectiveness of shorter courses of metronidazole, at lower doses, which are used in Europe, is currently being evaluated."

Regarding the question of mutagenicity, Dr. Schmidt stated: "Mutagenicity testing is a very important new area of drug evaluation. At the present time, however, it is premature to use the results of such testing to draw conclusions regarding the safety of drugs for human use. This is particularly true for mutagenicity testing in submammalian systems. Regarding our present ability to interpret mutagenicity data obtained in microbial testing systems, Dr. Samuel S. Epstein said: '. . . the presumptive relevance of such data to man is highly questionable. . . .There is an enormous range of differences in the body chemistry, metabolism, et cetera, that make it untenable to extrapolate directly from nonmammalian systems to mammalian systems using *in vivo* methods.' (Testimony before the Senate Subcommittee on Executive Reorganization and Government Research; April 6, 1971.)"

It is hoped that this information will clarify the points raised by Dr. Grabowski—both for him and for readers of the JOURNAL.

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## Ampicillin Resistant Hemophilus Influenzae Type B in the West

TO THE EDITOR: In March 1974, the first report of meningitis caused by ampicillin resistant hemophilus influenzae type B was published from the Center for Disease Control.[1] Sensitivity studies revealed that on ampicillin disk testing, these organisms had less than an 8 mm clear zone, whereas sensitive strains had greater than a 20 mm clear zone, and on tube dilution studies these organisms had greater than 8 μg per ml minimum inhibitory concentration, whereas sensitive strains have less than 2 μg per ml minimum inhibitory concentration.

Previously, there had been case reports of failure of ampicillin to eradicate H. influenzae type B but on examination it was found that no cases of drug-resistant strains were validated, but rather inadequate dosage, inappropriate route of administration or compromised host defense was found.

Since the report in March 1974, many case reports of ampicillin resistant Hemophilus influenzae type B infections have been published from the eastern United States. This development of resistance was associated with production of beta-lactamase, the presence of which can be bioassayed. In Atlanta in July 1974, out of 25 isolates from blood or cerebrospinal fluid (CSF), 16 were found resistant to ampicillin and found to require a minimum bactericidal concentration greater than 12 μg per ml, whereas it is known that CSF levels greater than 5 μg per ml are difficult to obtain.[2] In a report from Washington, DC, 10 percent of isolates during the first half of 1974 were found beta-lactamase positive and ampicillin resistant.[3]

In Denver in 1974, a report of 83 children with Hemophilus influenzae infections at three pediatric hospitals showed no resistant organisms,[4] and not until the spring of 1975 were there reports from Denver, at the Society for Pediatric Research Meetings, that a resistant organism was isolated from children with disease.

In Los Angeles, surveillance of *in vitro* susceptibility of isolated strains to ampicillin and chloramphenicol immediately commenced, after publication of these reports of resistant Hemophilus influenzae type B, and results were compared with those of sensitivity studies of isolates obtained a decade earlier.[5] All isolates from 1974 were beta-lactamase negative and uniformly were sensitive to both antibiotics. However, after submission of their article in 1975, these same workers obtained an isolate from a child with meningitis treated in Pasadena who was resistant to ampicillin and produced beta-lactamase.

In San Francisco, since these reports were noted in 1974, surveillance of Hemophilus influenzae type B has been carried out at Children's Hospital of San Francisco (with bacteriology studies done by Dr. Wie-Shing Lee), and no cases of meningitis or septicemia due to beta-lactamase producing ampicillin resistant organism were noted from January 1974 to October 1975.

In October 1975, an 18-month-old boy developed septicemia, pneumonia and empyema from which Hemophilus influenzae type B were